Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Accompanying this submission is a Petition for Extension of Time, Sequence Listing, and Statement confirming that the Sequence Listing can be entered without introduction of new matter. Because the statutory deadline fell on a Sunday, this submission is timely under 37 C.F.R. §1.7.

The specification has been amended to refer (by SEQ ID NO) to the Sequence Listing, and also to conform the specification to U.S. practice. Because no new matter has been introduced, entry of these amendments is respectfully requested. The objection to the specification should therefore be withdrawn.

Claims 1, 7, 9, 16, 22, 23, and 25 have been amended, and claim 24 has been canceled without prejudice. Claim 1 has been amended to incorporate the preamble language into the body of the claim, to more specifically define the GMCSF derivative, and to specify that the tolerance is induced to treat or prevent an aberrant or undesired immune or inflammatory response to the antigen. Descriptive support for the GMCSF derivative limitation appears at page 12, line 1 to page 15, line 14, particularly at page 12, lines 19-21, and page 13, lines 22-26. Descriptive support for the "whereby clause" appears in the preamble to claim 1 and at page 23, lines 25-29. No new matter has been introduced. Claims 1-10, 12-14, 16, 20-45, 47-49, 51, 66, 67, 69, 73-75, 78, and 79 remain pending. Claims 1, 2, 5-10, 12-14, 16, 22, 23, 25, and 26 are under examination, and all other claims stand withdrawn.

Applicant respectfully requests reconsideration of the lack of unity objection. On pages 2-3 of the office action, the U.S. Patent and Trademark Office ("PTO") asserts that the claims merely recite a newly discovered result. Applicant respectfully disagrees, because the claimed method constitutes a patentable new use.

The PTO has failed to demonstrate that the claims lack a special technical feature (i.e., under PCT Rule 13.2) over Piquet-Pellorce et al., "Prostaglandin E2 Potentates Granulocyte-Macrophage Colony Stimulating Factor-Induced Histamine Synthesis in Bone Marrow Cells: Role of cAMP," *Life Sci.*, 48:2377-2382 (1991) ("Piquet-Pellorce"). Because the PTO acknowledges that Piquet-Pellorce is silent regarding inducing tolerance to an antigen, Piquet-Pellorce cannot destroy the novelty of the claimed invention. Indeed, claim 1

was never rejected under 35 U.S.C.§ 102 over Piquet-Pellorce. For this reason, the lack of unity rejection is improper and should be withdrawn. Applicant therefore requests examination of all currently withdrawn claims.

The rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

On pages 4-7 of the office action, the PTO alleges that the specification is enabling for a method of inducing tolerance to an antigen by administering PGE and GMCSF, but not for any other agent that raises the effective cAMP concentration in a monocyte cell together with GMCSF. The PTO has based this conclusion on the allegation that the present application only provides experimental support in relation to the combination of PGE and GMCSF. Applicant respectfully submits that the PTO is incorrect, because both forskolin and probenicid were shown to have similar biological effects, at least in relation to IL-10, when used in combination with GMCSF (*see* Figures 6 and 9). What these three agents have in common is their ability to raise cAMP levels in a monocyte cell (*see* Figure 5). Applicant submits that the description of results using these three agents (that achieve the recited effect) fully enables the recited language. Moreover, given the identification of these three agents, persons of skill in the art would fully expect that other agents that raise cAMP levels in a monocyte cell will have the same effect in combination with GMCSF. Thus, the claim language "an agent which raises the effective CAMP concentration in a monocyte cell" is fully supported by the present application.

On page 7 of the office action, the PTO alleges that the claims are enabled only for inducing tolerance to the antigen HLA-A2 for combating transplant rejection, and therefore it would require undue experimentation to determine which other antigens could be administered. Applicant respectfully disagrees. Pages 26-30 of the application list a large number of antigens that can be used with respect to specific conditions to be treated or prevented. Given the recitation of specific antigen useful for inducing tolerance for specific conditions, persons of skill in the art would be able to practice the invention without undue experimentation. Thus, the claim language "antigen" is fully supported by the present application.

On pages 9 and 10 of the office action, the PTO alleges that there are substantial scientific reasons to doubt that the claimed invention would work with respect to reducing tolerance to all antigens, and in particular whether this extends to treating any autoimmune diseases. The PTO asserts that, with respect to the treatment of autoimmune

disease, *in vitro* tests are not predictive of success *in vivo*. However, the PTO has provided no support for this position (and not demonstrated that the examiner can take notice of this asserted "fact"). Therefore, the assertion cannot be accepted as true. For this reason, applicant submits that the PTO has failed to demonstrate that the present application is not enabling for inducing tolerance to antigens associated with autoimmune disease.

For all these reasons, applicant respectfully submits that the enablement rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 is improper and should be withdrawn.

The rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 under 35 U.S.C. § 112 (1st para) for lack of written descriptive support is respectfully traversed.

The PTO asserts on pages 10-12 of the office action that the application only provides descriptive support for the GM-CSF of SEQ ID NO: 2. Applicant respectfully disagrees, because the PTO has failed to consider the state of the art at the time the present invention was made. In fact, a number of GM-CSF variants/derivatives were known in the art, including those described in the application at pages 12-14 as well as those described in PCT Publ. WO 1989/010403. In addition, GM-CSF from various mammals were also known (see, e.g., Genbank Associates CAA26821, mouse; NP 776452, bovine; BAA04649, pig; AAG16626, rhesus monkey). Thus, persons of skill in the art would have understood that GM-CSF is not limited to the human GM-CSF of SEQ ID NO:2.

Moreover, the comparison of the facts of this case to the caselaw cited on pages 11-12 is inapposite because the facts, here, are very different. As noted above, the persons of skill in the art fully appreciated the various GM-CSF and derivatives that were known in the art, whereas the cited caselaw involved claims to novel products or use of novel products where only a single species (or in some cases, no species) were disclosed. That is clearly very different from the circumstances here, where a relatively large number of species were previously known in the art.

Because persons of skill in the art fully appreciated the meaning and scope of GM-CSF, and applicant demonstrated possession of the claimed method, the present application provides sufficient descriptive support for the claimed method. The written description rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 should therefore be withdrawn.

The rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 under 35 U.S.C. § 112 (2nd para) for indefiniteness is respectfully traversed in view of the above amendments and the following remarks.

Claim 1 is not indefinite due to the recitation of the term "an antigen." As described in the application, this invention is clearly applicable to many different antigens, and to limit the claim to specific antigens would not be appropriate. Merely because a claim term is broad does not render its meaning indefinite. This basis of rejection should be withdrawn.

Claim 1 clearly recites the method step of "administering to a patient…". This basis of rejection should therefore be withdrawn.

The rejection of claim 1 for failing to identify the condition that the patient is suffering from is overcome by the above amendment. As described in the application, this invention is clearly applicable to various different patients, each of whom requires tolerance to different antigens. The conditions are associated with either aberrant or undesired immune or inflammatory response to the antigen. This basis of rejection should be withdrawn.

The rejection of claims 1, 22 and 25 for use of the term "GMCSF or a derivative thereof" is overcome by the above amendment. The specification clearly recites that GMCSF or its variants or derivatives can be used to practice the invention, and defined these derivatives as a fragment, fusion or sequence variant of GMCSF that has at least 50% of the ability of full length GMCSF to stimulate the production of granulocytes and macrophages from their progenitor cells and which in the presence of prostaglandin E causes monocytes to express IL-10. This is clearly defined in the specification. Therefore, this basis of rejection should be withdrawn.

Because the elected species is allowed for the reasons noted herein, the PTO must expand the scope of the search to consider other species. Moreover, the recitation of non-elected species does not render the claim language indefinite. This basis of objection should be withdrawn.

The rejection of claim 6 for recitation of "or an analogue thereof" is respectfully traversed. Prostaglandin analogues are very well known in the art, and many examples are given in the specification on pages 10 and 11. It is also well known and well appreciated that prostaglandin analogues must retain the basic prostaglandin structure to be considered to be a prostaglandin analogue. This is evidenced by the fact that "prostaglandin analog" is a term that is widely used in the art—*see* U.S. Patent Nos. 4415501, 4543421, 4588741, 5260449, 5409911, 6482990, 5820587 (at claim 50), 5908853 (at claim 8), 6031002 (at claim 15), 6342524 (at claim 1), 6486208 (at claim 15), 6632451 (at claim 35), and 7423141 (at claim 5). (Because these references are widely available to the PTO, they

are not attached hereto.) Because persons of skill in the art fully appreciate the meaning of "prostaglandin analogue," this basis of rejection should be withdrawn.

The rejection of claims 9, 16, 22, and 25 for recitation of "an antigen or derivative thereof" is overcome by the above amendments. This basis of rejection should be withdrawn.

For all these reasons, the rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 for indefiniteness is improper and should be withdrawn.

The rejection of claims 1, 2, 5-9, 12-14, 16 and 22 under 35 U.S.C. § 103(a) for obviousness over Piquet-Pellorce in view of U.S. Patent No. 5,581,784 to Owens et al. ("Owens") is respectfully traversed.

Piquet-Pellorce teaches that the administration of PGE2 and GMCSF to isolated bone marrow cells increases intracellular cAMP levels. The PTO has acknowledged that Piquet-Pellorce is silent regarding inducing tolerance to an antigen. Owens is cited for teaching that PDE IV selective inhibitors, such as rolipram, also increase intracellular cAMP levels.

Applicant submits that the PTO has failed to set forth a *prima facie* basis for this rejection. The combination of references fails to teach or suggest each and every limitation of the claimed invention. In particular, the combination of references fails to teach or suggest the administering of PGE2 and GMCSF to a patient, let alone where such administering is effective induce tolerance to an antigen in the patient and thereby treat or prevent an aberrant or undesired immune or inflammatory response to the antigen. Because neither of these limitations is taught or suggested, the rejection of claims 1, 2, 5-9, 12-14, 16 and 22 for obviousness over Piquet-Pellorce in view of Owens is improper and should be withdrawn.

The provisional rejection of claims 1, 2, 5-10, 12-14, 16, and 22-26 on the basis of non-statutory, obviousness-type double patenting over U.S. Patent Application Serial No. 10/576,437 is moot, because the cited application has been abandoned. This rejection should therefore be withdrawn.

In view of all the foregoing, it is submitted that all the claims are in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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